UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

002136

MEMORANDUM 21-May-1982

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Robert J. Taylor, PM #25
Registration Division (TS-767)

SUBJECT: PP #1G2502, FAP #1H5206 (Dicamba) and
PP #1G2519, FAP #1H5305 (Chlorflurenol) Experimental
Use on Cotton-Caswell #192A and #295

FROM: Stephanie April, Ph.D. Stephanie April
Toxicology Branch/HED (TS-769)

THRU: William Butler, Section Head William Butler
Review Section #3
Toxicology Branch/HED (TS-769)

Action Requested:

A review of the submitted toxicity data for dicamba as outlined in R. Coberly memo of August 18, 1981.

Sponsor:

Velsicol Chemical Corporation
Chicago, Illinois

Recommendation:

In consideration of the extensive data base both previously reviwed and presently submitted and reviewed, and the very limited exposure via diet and application, the temporary tolerance for dicamba is supported.

Previously Reviewed Studies:

The toxicology data base reviewed in connection with the current action include but are not limited to those cited in the memo of August 20, 1981, from R. Coberly (TS-769) to R. J. Taylor (TS-767).

Review of New Studies From Present Submission:

A. Primary Dermal - Rabbit

Technical Banvel, BioResearch Lab Ltd., Senneville, Quebec, #12663, Accession #070030, July 15, 1980.

1

002136

Material Tested:

Banvel 4S liquid in a patch.

Materials and Methods:

Six male New Zealand White rabbits (Oryctologus cuniculus), 2.1 to 2.6 kg and 10 to 13 weeks old were individually housed at 22 ± 2°C for a two-week acclimatization period with food (Purina Rabbit Chow 5322) and water ad libitum. The animals were shaved and abraded in two sites. The test material was applied to two intact and two abraded sites each. The sites were covered with a rubber dam for 24 hours at which time the dam was removed and the excess material wiped off. The animals were observed for 9 days.

Each animal was scored (on the basis of erythema/edema) at each observation period to enable the establishment of an individual primary dermal index. The group score is the mean of the individual scores.

Results:

The average score was 3.7/8.0. Both edema and erythema were established in 24 hours. Edema disappeared in 5/6 animals in 5 days while erythema disappeared in the same 5/6 animals in 7 days. Only a slight difference was observed between abraded and intact sights.

Conclusion:

Banvel 4S liquid is a mild dermal irritant in albino rabbits.

Classification: Core Minimum

Toxicity Category: IV

B. Primary Eye Irritation - Rabbit

Technical Banvel, Bio-Research Lab Ltd., Senneville, Quebec, #12662, Accession #070030, July 16, 1980.

Material Tested: Banvel 4S liquid

Materials and Methods:

Nine male New Zealand White rabbits (Oryctologus cuniculus), 2.0 to 3.5 kg, and 10 to 13 weeks old, were used. The test animals were housed individually at 22°C ± 2°C for a two weeks and fed Purina Rabbit Chow 5322 and water ad libitum.

The animals were randomized by a computer number generator. Three animals were initially examined for corneal injury by the use of the fluorescein dye procedure. Group I consisted of 3 animals whose eyes were irrigated while Group II had 6 animals with unwashed eyes.

2

The test material was administered once at 0.1 ml of the undiluted Banvel 4S. The scoring, according to the method of Draize, was done at 24, 48, 72 and 96 hours and 7, 10 and 13 days.

Results:

Irrigated group: Mild to moderate erythema of the palpebral conjunctiva with moderate periorbital discharge. Mild transient corneal opalescence.

Non-irrigated group: Mild to moderate corneal opalescence over 50 to 100% cornea; moderate eyelid erythema of the palpebral conjunctivae, moderate eyelid edema and periorbital discharge. All but one animal recovered in 7 days.

Conclusions:

Banvel 4S can be considered a mild to moderate ocular irritant in male albino rabbits from this data.

Classification: Core Minimum

Toxicity Category: III

C. Subchronic 21-day Dermal in Rabbits

1. Technical Banvel, IRDC #163-620, Accession No. 070030, October 30, 1979.

Material Tested:

Technical Banvel 4S Liquid

Material and Methods:

Sixteen male and female New Zealand White rabbits, 1.8 to 2.5 kg, were housed individually at constant temperature, humidity and light with food and water ad libitum for two weeks prior to initiation of the study. During this incubation period Triple Sulpha (0.11% to 0.02%) was administered in drinking water as a disease prevention measure.

The animals were divided into treatment groups using a computer-generated random number table.

Dose Banvel Mg/Kg/Day	Vol. Ml/Kg	No. Rabbits M	No. Rabbits F
0	2.1 (0.9% NaCl)	4	4
100	0.08	4	4
500	0.42	4	4
2500	2.10	4	4

The test material was applied with a syringe and spread evenly with a glass rod over the clipped dorsal area of the body for 6-hours per day, 5 days per week for three weeks. At the 6 hour exposure time each day, the excess material was removed and the dermal irritation scored.

Blood samples prior to testing and at 3 weeks were used for hematology and blood chemistry. Urinalysis was also done.

Results:

Eight animals died on test including two controls, 2 at 500 mg/kg/day and 4 at 2500 mg/kg/day. Some of the antemortem observations of the control and 500 mg/kg/day included distended abdomen, anorexia, diarrhea, hypoactivity, and cyanosis. The treated animals that died on test at 500 and 2500 mg/kg/day were observed to have nasal discharge, ataxia, dehydration and loss of righting reflex.

Dermal irritation was observed in all treated groups from very slight erythema and edema at 100 mg/kg/day to moderate edema and erythema at 2500 mg/kg/day.

Only the 2500 mg/kg/day females had a statistically significant difference in mean body weight loss from the controls. This group also was the only group where there was a decrease in hemoglobin concentration and a total blood protein decrease.

There were no other hematology, blood chemistry or urinalysis effects in this study.

Conclusion:

No compound related changes were seen in general behavior and appearance, biochemical studies and urinalysis.

Classification: Core Minimum

2. Technical Banvel, IRDC, #163-618, Accession No. 070030, August 22, 1979.

Material Tested:

Technical reference standard Banvel 86.8%, Lot 52625110.

Material and Methods:

Refer to previous study described above. The protocol is exactly the same for this study as IRDC #163-620.

Results:

Seven rabbits from control and test groups died or were sacrificed in extremis during the study although these events were not considered compound related.

There were no Banvel related changes in general behavior, appearance, body weight, or in blood and urine analysis. At the low dose (100 mg/kg/day), erythema was slight in intact and slight to moderate in abraded animals in weeks 2 and 3. There was also slight edema, atonia, desquamation, coriaceousness and fissuring.

At 500 mg/kg/day, the erythema in the 2nd week was moderate, subsiding to slight to very slight. The edema and other effects were slight to moderate in the intact and moderate in the abraded.

At 2500 mg/kg/day, the erythema was moderate to severe while the other skin effects were slight to moderate.

There were no compound related gross pathology lesions in the test animals. The histopathological examination revealed only skin lesions. There were no significant organ weight changes.

Conclusions:

Dermal application of Banvel results only in skin toxicity.

Classification: Core Minimum

D. Subchronic Oral Toxicity

Technical Banvel (Dicamba), IRDC, #163-671, Accession No. 070030, November 11, 1980. 13-week Oral Toxicity in Rats.

Material Tested:

Technical Banvel 86.82%, Beige Chips, Lot No. 52625110.

Material and Methods:

This study follows a 4-week pilot study in rats using dietary dosage levels of 5000, 7500, 10000, 12500 and 15000 ppm in 5 males and 5 females at each level. Based on the results of this study, a 13-Week Dietary Toxicity Study in rats was done on 20 male and 20 female rats at each of the following dosages: 1000, 5000 and 10000 ppm and 0 ppm.

The rats used were Charles River CD (111-164g) which were preconditioned at controlled temperature, humidity and light in individual cages and maintained with ad libitum water and Ralston Purina Rodent Chow #5002.

The animals were observed twice daily for appearance, behavior, mortality, body weight and food consumption. Clinical tests, including hematology, biochemistry and urinalysis, were performed.

002136

At termination of the study pathological examination consisted of gross pathology, organ weights and histopathology.

Results:

In the range finding study, there was impaired mobility in the hind extremities in one animal at 12,500 ppm and in 7 rats at 15000 ppm. The body weight gains and food consumption were slightly reduced at 12,500 ppm and moderately reduced at 12,500 and 15,000 ppm when compared with control rats. There was no mortality.

In the 13-week feeding study there was no compound related changes in general behavior and appearance. Three female rats died on study (one control, one mid-dose and one high-dose). There was a slight decrease in comparative body weight gains and food consumption at 10000 ppm versus controls. There were no gross lesions or organ weight variations in the treated groups. There was an absence or reduction of cytoplasmic vacuolation of hepatocytes in the high-dose groups. NOEL = [redacted] ppm (systemic)

Classification: Core minimum

E. Chronic Study, ~~rats~~ mice

Technical Banvel, IBT #8580-10130, 24-month chronic oral toxicity study in Charles River CD-1 ~~rats~~ mice, May 16, 1980, and March 30, 1981. Accession No. 070030.

This study is an unvalidated IBT study which cannot be utilized at this time.

F. Metabolism

1. Technical Dicamba, Distribution and Excretion in Rats, by Radiotracer Technique, R.Tye and Engle, D., J. Agr. Food Chem., 15, 837-840 (1967). Accession No. 070030, 1967.

Material Tested:

C^{14} labeled in carboxyl position Dicamba 98% pure.

Methods:

Groups of 4 males and 8 females per dose of Charles River CD rats (6 months) received a single oral dose (0.1 or 0.93 gm/kg) in peanut oil by esophageal intubation. The rats were sacrificed at intervals ranging from one hour to 72 hours after dosing. Tissues, urine and blood were retained for subsequent analysis.

One male and one female Charles River CD rat, 7 months old, received a single injection subcutaneously of C^{14} labeled Dicamba. The rats were sacrificed at 72 hours. Urine and feces were retained for analysis.

002136

Groups of 5 male and 5 female rats housed in individual metabolic cages were fed C^{14} labeled Dicamba at 10, 100, 1000, 10000 and 20000 ppm for 24 days. Rats were sacrificed at 1, 3, 6, 13 and 24 days. Tissues and excreta were retained for analysis.

Results:

Excretion of intact dicamba and the glucuronide of dicamba was nearly 100% when administration was by dermal application or subcutaneous injection. Dietary ingestion resulted in 96% urinary excretion in 48 hours and 4% via the feces. Fairly equal tissue distribution occurred initially but tissue levels did not persist beyond a few hours indicating no bioaccumulation.

Classification: Core Minimum

2. Technical Dicamba, Metabolism in Rats, Whitacre, D.M. and L.I. Diaz, Accession No. 070030, Environmental Sciences, 1976, #480068-1.

Material tested:

C^{14} dicamba

Method: Two female Holtzman rats, 176 g housed in individual metabolism cages after a single oral dose of dicamba. Urine and feces were analyzed.

Results: 88% of the unchanged dicamba was excreted in the urine in 96 hours. 2-3% was eliminated in the feces. The tissues and CO_2 were not analyzed.

Classification: Supplementary

3. Technical Dicamba, Metabolism in Mice, Rats, Rabbits and Dogs, L.I. Diaz and D. Nietschomann, Environmental Sciences, Velsicol #480068-8. Accession #070030, 1980.

Material Tested:

≥99% pure dicamba -C^{14}

Methods:

Six Sprague Dawley albino rats, 320-349 g, housed individually, were administered a single oral dose of 102 mg/kg radiolabelled dicamba. Four Swiss albino mice, 26-38 g, received a single oral dose of 89 mg/kg C^{14}-dicamba. Four New Zealand white rabbits, 2.0-2.138 kg, were given a single oral dose of 100 mg/kg C^{14} dicamba. Five beagle dogs weighing 8.7 to 11 kg received 88.2 mg/kg C^{14} dicamba. Each species had a control animal receiving only the vehicle. All animals were fasted 8 hours for rats and mice and 12 hours for rabbit and dog prior to dosing by oral intubation. Animals were sacrificed at 16 and 96 hours. Blood, urine, feces and tissues were collected and analyzed.

Results

Most of the unchanged dicamba was eliminated in 16 hours in the urine of all four species - 90% in four days. Feces elimination accounted for 0.6% dogs, 2.5% rats and rabbits and 9% in mice. Small amounts of O-demethylated dicamba was also found in the excretions.

Classification: Core Minimum

4. Technical Banvel, Metabolism in Dairy Cow, St. John, L.E. and Lisk, D.J., Cornell Pesticide Residue Laboratory, J. Dairy Sci. 52(3)392 (1969). Accession No. 070030.

Material Tested:

A Holstein cow was dosed with 5 ppm Banvel daily for five days. Milk, urine and feces were collected daily for analysis.

Results:

73% intact Banvel was excreted in the urine in 7 days. No residues were detected in the feces and milk.

Classification: Supplementary

5. Technical Banvel, Metabolism in the Lactating Cow, Oehler, D.D. and Ivie, G.W., J. Agric. and Food Chemistry, Vol. 28, July/Aug. 1980. Accession No. 070030.

Material Tested: Radiolabeled Dicamba C^{14}

Material and Methods:

A 411 kg lactating Jersey cow was administered 450 mg C^{14} at 12 hours intervals 11 times, equivalent to 2.2 mg/day and 60 ppm. Urine and milk were collected for analysis as were feces and tissues on sacrifice.

Results:

In 5 days, 99% label was excreted in the urine, 1.5% in the feces and 0.02% in the milk. Only very low levels were found in the tissues. No retention of the dicamba was found.

Classification: Supplementary

END